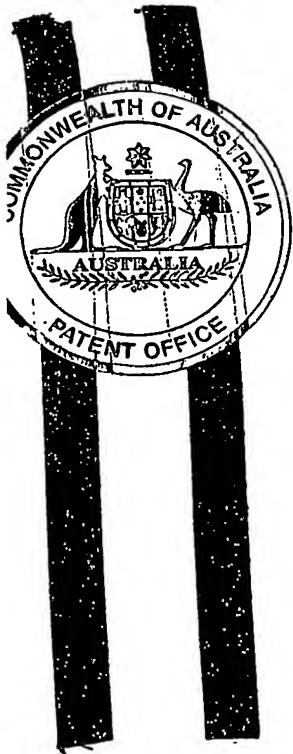REC'D **2 4 AUG 2004**

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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003904100 for a patent by THE UNIVERSITY OF QUEENSLAND as filed on 05 August 2003.

WITNESS my hand this
Seventeenth day of August 2004

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TEAM LEADER EXAMINATION
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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: "APPARATUS AND METHOD FOR
EARLY DETECTION OF
CARDIOVASCULAR DISEASE
USING VASCULAR IMAGING"

The invention is described in the following statement:

TITLE

APPARATUS AND METHOD FOR EARLY DETECTION OF

CARDIOVASCULAR DISEASE USING VASCULAR IMAGING

FIELD OF THE INVENTION

5   The present invention broadly relates to a method and apparatus
for detecting early cardiovascular disease. In particular, this invention
relates to an apparatus and method utilising vascular imaging techniques.

BACKGROUND OF THE INVENTION

Cardiovascular disease (CVD) is the leading cause of disability and
10   death in the western world, resulting in more premature deaths than any
other illness. Unsurprisingly, treatment of CVD represents the highest cost
burden to any healthcare system. Accordingly, there is tremendous social
and political pressure to develop earlier and more reliable diagnostic tests
to assist in the detection, treatment and prevention of CVD.

15   Changes in the structure and function of blood vessels are known
to be an early stage indicator in the development of CVD. This suggests
that tests of vascular function may be used to diagnose early disease and
track the response to various treatments that cause disease regression.

Coronary angiography and stress testing, which have been the
20   cornerstone of the diagnosis and management of coronary artery disease,
are ineffective in diagnosing early sub-clinical disease because they
depend on the detection of luminal narrowing, while early disease causes
vessel expansion. Although angiography may be used to identify earlier
lesions, it does not directly assess the vessel wall unless intravascular

ultrasound is performed. This is invasive and expensive. Various invasive techniques have been used to examine endothelial function in patients with coronary artery disease. However, these are ill-suited to sequential follow-up, and being invasive, carry the potential of significant adverse

5   effects.

The most widely used non-invasive testing is brachial artery reactivity (Celermajer DS *et al.* Lancet 1992;340:1111-5). However, in using this method, the measurement of flow-mediated vasodilation is technically challenging. Normal ranges show large standard deviations, in

10   part because the results are influenced by a number of acute stimuli, including the fasting state, tobacco, caffeine and vasoactive drug loads. Unfortunately, the presence of both vascular disease and risk factors influence the result.

Another technique which has been developed is applanation

15   tonometry (Hayward CS *et al.* Hypertension,2002;40:e8-e9). This non-invasive clinical tool measures the elastic properties of the entire arterial tree, reflecting systemic vascular changes. Applanation tonometry uses a transcutaneously-applied micromanometer tipped probe which is placed against an arterial wall. When there is sufficient pressure to distort, or

20   applanate the artery, it creates a signal which approximates instantaneous arterial pressure. The signal is then digitised and reconstructed on a PC. This application is most feasible over distal vessels, such as the radial artery with minimal soft tissue cover and an underlying bony surface to support it, rather than over the proximal vessels, *eg.* the carotid arteries,

which are embedded in adipose tissue and muscle and do not have the same support structure and therefore are subject to movement and subtle pressure changes. While central aortic pressure is assumed to be equal to carotid pressure because of the proximity of the vessels, carotid tonometry is technically challenging and suffers from test-retest variability. Although the radial technique is less limited by these problems, the use of a transfer function to reconstruct a central waveform may be particularly problematic in the elderly or women. A further limitation is that medical specialists who are most likely to use the data are unfamiliar with the technology. Applanation tonometry requires specialist equipment and training, which have both compromised the uptake of the technique.

Another non-invasive method is total arterial compliance (TAC) (eg. Segers et al. Ann Biomed Eng 1999;27:480-5). TAC measures systemic distensibility based on the pulse-pressure method derived from the two-element Windkessel model, i.e. the increment of volume of the systemic arterial bed for an increment in distending pressure of the entire systemic arterial tree. Compliance falls with the loss of elastic function in the great vessels, as occurs in conditions such as hypertension and atherosclerotic vascular disease. Several approaches have been used to measure TAC. One such technique requires simultaneous measurement of stroke volume and arterial pressure, with the TAC value (mls/mmHg) being derived mathematically from three separate measurements: tonometry for pressure, 2D echo for orifice area and Doppler for flow.

In recognising the need for non-systemic direct measurement of vessel wall displacement, techniques using M-mode (Gamble *et al.* Stroke 1994;25(1): 11-16) and radiofrequency signals (Hoeks *et al*, Ultrasound Med Biol 1990; 16(2): 121-8) have been explored. However both techniques have shown to be highly complex and highly dependent on two-dimensional image quality when used clinically.

Another method, Doppler echocardiography is used traditionally to evaluate the velocity and direction of blood flow in the heart and vessels. Recent technical developments have allowed reduction of the wall filters and scale, thus permitting the evaluation of low velocity, high amplitude signals which come from tissue. Colour tissue Doppler imaging (TDI) is a technique in which the velocity of myocardial movement toward the transducer is displayed in colour-coded form on myocardial images. Advantageously, this technique permits rapid, simultaneous visualisation of several walls, either myocardial or vascular, in a single view. However, this method does not (i) provide for means of assessing local vascular behaviour, but rather systemic measurements or (ii) consider the influencing factors of distensibility or blood pressure.

Accordingly, there exists a need for the development of a simple, accurate means of assessing direct or local vascular elasticity that will allow for early detection of arterial disease and will provide a tool for monitoring outcomes of treatment and preventive medicine.

OBJECT OF THE INVENTION

Accordingly, it is an object of the invention to provide an apparatus and method using Doppler imaging to overcome one or more of the problems of the prior art or provide a useful commercial alternative.

SUMMARY OF THE INVENTION

According to the present invention there is provided a method for determining local arterial elasticity for early detection of cardiovascular disease including the steps of:

(i) acquiring velocity data from arterial colour tissue Doppler imaging;

(ii) processing the velocity data to generate arterial displacement data;

(iii) calibrating the arterial displacement data using blood pressure; and

(iv) identifying significant features in the calibrated arterial displacement data to generate a local elasticity measurement.

Preferably, the step of calibrating the arterial displacement data uses mean and diastolic brachial cuff blood pressure.

Still preferably, the step of identifying significant features includes using the features of peak aortic ejection and peak pulse pressure in the calibrated arterial displacement data.

Still more preferably, the step of identifying significant features includes using the features of the beginning and end aortic ejection peaks in the calibrated arterial displacement data.

According to a second aspect of the present invention there is provided an apparatus for determining local arterial elasticity for early detection of cardiovascular disease comprising:

an ultrasonic signal source directing ultrasound signals at an artery;

5   an ultrasonic signal receiver receiving ultrasound signals reflected from or transmitted through the artery;

means for analysing signals received by ultrasonic signal receiver to extract Doppler imaging data;

means for acquiring blood pressure data;

10   signal processing means for calibrating said Doppler imaging data using the blood pressure data; and

means for identifying significant features in the calibrated arterial displacement data to generate a local elasticity measurement.

BRIEF DESCRIPTION OF THE DRAWINGS

15   In order that the present invention may be more readily understood and placed into practical effect, preferred embodiments of the invention will be described, by way of example only, with reference to the accompanying drawings, in which:

FIG. 1 is a diagram of the method of the invention showing the

20   steps for the generation of local elasticity measurements.

FIG. 2 is a schematic diagram of an apparatus for early detection of cardiovascular disease using the arterial imaging of FIG. 1.

FIG. 3 shows the output from analysed arterial colour tissue Doppler with displacement curves for each cardiac cycle (bottom left) and mean displacement over time (top left).

FIG. 4 shows the output from Samtdi analysis program, where raw displacement curves (upper left), ECG (middle left) M-mode/TDI (lower left), averaged Doppler of the aortic outflow (lower right), averaged carotid tonometry (middle right) and calibrated displacement curves with tonometry (upper right) are displayed.

FIG. 5 is a table showing the strong correlation of pressure data obtained by arterial Doppler imaging and by tonometry methods.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring to FIG. 1, the method 10 of generating local elasticity data is broadly described. The initial step of acquiring tissue velocity data 12 is followed by the subsequent extraction of arterial displacement data 14 from the velocity data 12. Central blood pressure data 16 is acquired and used in the calibration 18 of the displacement data 14. Preferably, the blood pressure data 16 used is mean and diastolic brachial cuff blood pressure. Significant features 20 in the calibrated arterial displacement data are identified. Preferably, the significant features 20 are peak aortic ejection and peak pulse pressure. More preferably, the significant features 20 include the beginning and end aortic ejection peaks. The resultant data represents a local elasticity measurement 22.

FIG. 2 shows the early detecting CVD apparatus 24. In use, the apparatus 24 is connected to a patient 26 to measure waveform velocity data 28 as a measure of the local arterial elasticity 28. Specifically, the velocities derived from the smooth muscle layer as the artery expands in

5 systole and contracts in diastole are used to calculate arterial displacement, which is a measure of arterial elasticity 28. Arterial imaging data are acquired by directing ultrasound signals 30 at an artery of a patient 26 using an ultrasonic signal source 32. An ultrasonic signal receiver 34 receives ultrasound signals 36 that are reflected from or

10 transmitted through the artery of the patient 26.

The signals 36 received by the ultrasonic signal receiver 34 are analysed to extract Doppler imaging (waveform velocity) data 38. The present method of arterial tissue Doppler imaging (TDI) is used to measure the low velocity, high amplitude signals created by the tissue.

15 Data 38 is acquired using tissue-specific presets programmable in the ultrasound system (AWM preset; ATL5000, Philips/ATL Bothell WA, USA) to determine frame rate, image size, and pre- and post-processing values. When a sufficient area of the carotid artery of the patient 26 is seen, usually 2-10 cm from the bifurcation, the area is zoomed in 2D and then a

20 similar color Doppler zoom box is superimposed on the patient's artery 26 to cover the outer edges of the adventitia and surrounding tissue. Color gain is set to 100%, focus is set in or about the far (posterior) wall of the patient's artery 26 and the highest frame rate possible is achieved (usually 140-200 frames per second). Images 38 are acquired as digital cine-

loops consisting of 3-5 cardiac cycles and stored to 3.5" optical disk for off-line analysis. The best quality image between the anterior, lateral and posterior views is selected for use for image acquisition.

The image data 38 is analysed off-line using software programs 40 which integrate velocity with respect to time. A suitable software program 40 (eg. Arterial Wall Motion v2.0 (AWM), Philips/ATL, Bothell WA, USA) plots the arterial wall velocities of the entire colour Doppler sector over the cardiac cycles to reconstruct a central pressure waveform, thereby generating quantitative measurements from the arterial Doppler imaging velocity data 38 for arterial displacement (µm) over time as shown in FIG. 3. These velocity displacement data 42 can then be exported in a spreadsheet readable format for further analysis, eg. as csv or xls file formats.

In the preferred embodiment, the displacement data 42 are imported into a software program 44 custom written in MatLab (eg. Samtdi v1.0 SG Carlier).

Blood pressure data 46 is acquired from the patient 26 using a manometer 48 or any like pressure reading device 48 known in the art. Preferably, the blood pressure data 46 acquired is mean (2 x diastolic BP + systolic BP/ 3) and diastolic brachial cuff blood pressure.

Significantly, the displacement data 42 is analysed using software 44 with respect to the central blood pressure data 46, so that the resulting arterial displacement waveform data 50 is calibrated for blood pressure. Significantly, the only previous work involving the use of colour tissue

Doppler for this purpose did not consider or calibrate for central blood pressure, which clearly influences distensibility.

As shown in FIG. 3, significant features in the calibrated arterial displacement waveform data 50 are selected for software analysis for the

5 generation of values for arterial compliance and other haemodynamic measures using the Doppler and pressure data. With the use of cursors, peak aortic ejection and peak pulse pressure features are firstly identified. Subsequently, the beginning aortic ejection and end aortic ejection features are then identified.

10 Noteworthy, the resulting waveform 28 is analogous to that obtained by tonometry, however, rather than reflecting systemic blood pressure, the waveform advantageously reflects the local behaviour of the vessel wall. Furthermore, this new method eliminates the need of using a radial-aortic transfer function, as is required with radial tonometry.

15 The present invention anticipates that arterial displacement provides new information about elastic vessels that is not provided by known tests, which instead reflect endothelial function and systemic (rather than local) compliance.

Advantageously, this novel ultrasound-based method 10 can be

20 readily loaded as software onto existing echo-Doppler machines 32, 34 for acquisition of TDI images 38, for which cardiologists and physicians with vascular interests are familiar and already use widely. The analysis software 40, 44 can be easily loaded onto a PC for off-line analysis.

It will be appreciated by a person skilled in the art that the present invention is not limited to the embodiments described in detail herein, and that a variety of other embodiments may be contemplated which are nevertheless consistent with the broad spirit and scope of the invention.

5   In order to demonstrate the efficacy of the invention, the inventors have conducted a study of 75 patients and compared the elasticity measurements of the common carotid artery with those obtained by tonometry. The results are tabulated in FIG. 4 and show strong correlations between TDI and tonometry wave forms, without significant.

10   differences in the minimum, maximum, mean or median pressures. This provides support for the use of imaging of the common carotid arteries with tissue Doppler to simplify estimations of central arterial pressure used to calculate total arterial pressure.
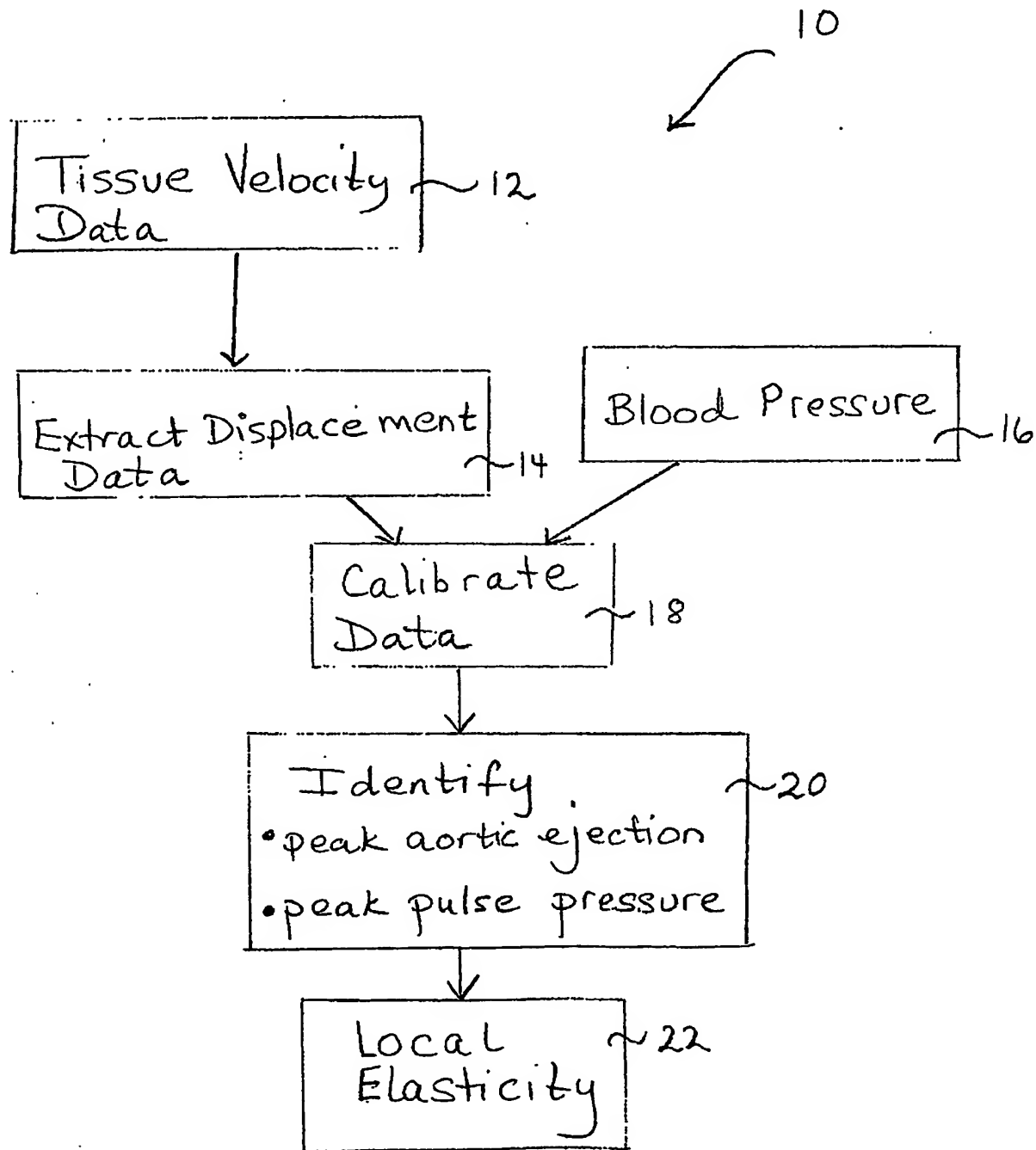
It is intended to demonstrate that measurement of elasticity with

15   TDI is abnormal in pathologic states, corresponds to the physical properties of vessels, and changes with therapy. It is also anticipated that using this method, a validated, easily-performed imaging technique to assess arterial dysfunction will be of value in facilitating the early diagnosis of vascular disease in those at risk, as well as in following a
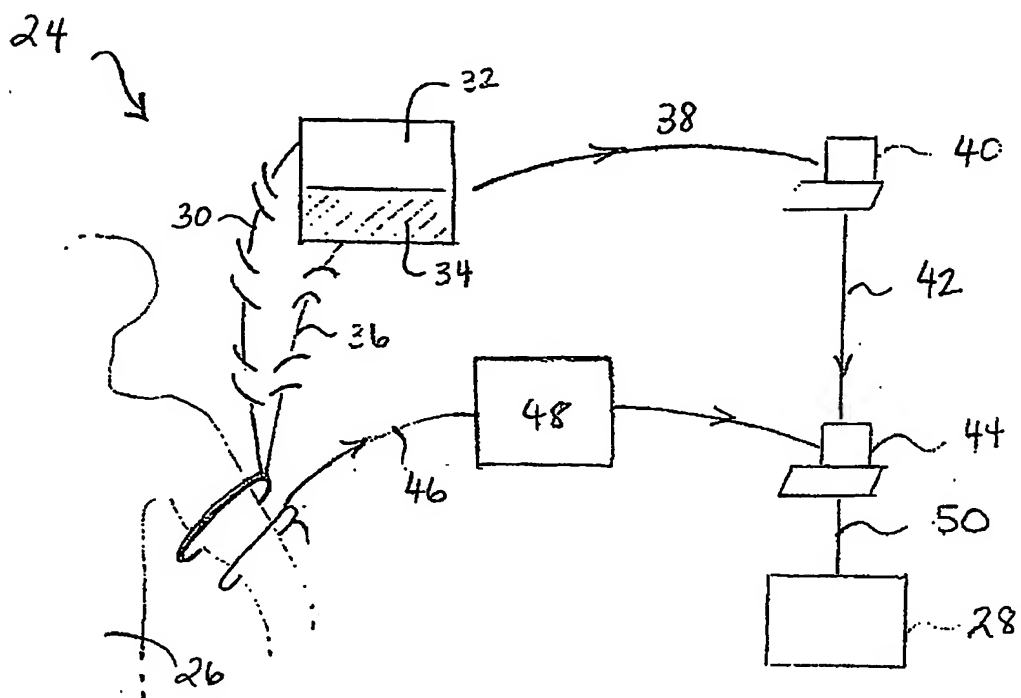
20   patient's response to therapy.

DATED this fifth day of August 2003

THE UNIVERSITY OF QUEENSLAND

By their Patent Attorneys

FISHER ADAMS KELLY

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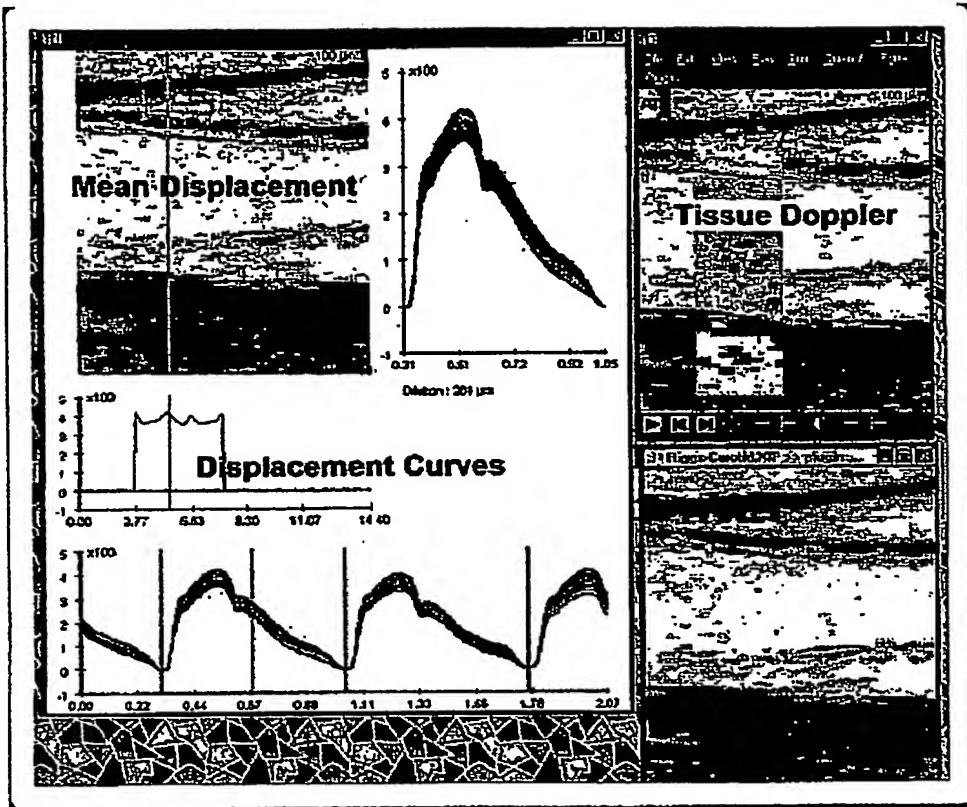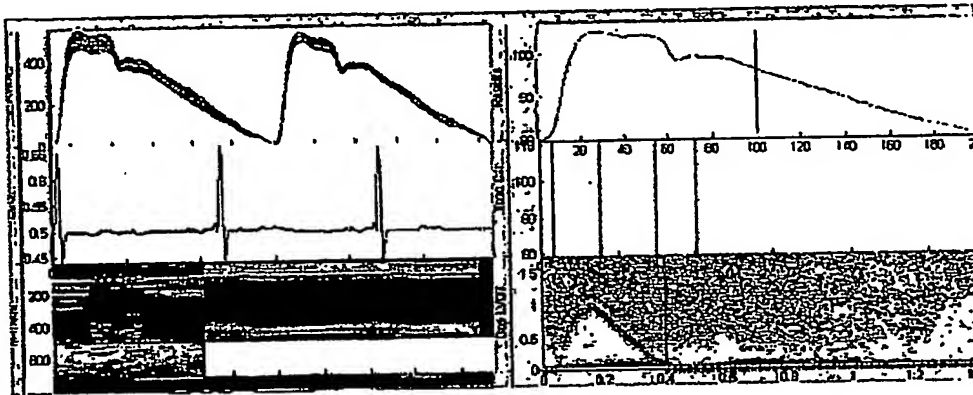Tissue Velocity Data ~12

Extract Displacement Data ~14

Blood Pressure ~16

Calibrate Data ~18

Identify
• peak aortic ejection
• peak pulse pressure
~20

Local Elasticity ~22

FIG. 1

24

32

30

34

36

38

40

42

48

46

44

50

28

26

FIG. 2

FIG. 3

5

FIG. 4

5

	Tono	TDI	r	p	DIFF
Min (mmHg)	76± 11	75± 11	.99	<.0001	1.3± 1.3
Max (mmHg)	113± 23	108± 18	.83	<.0001	5± 13
Mean (mmHg)	92± 13	92± 13	1.00	<.0001	-.01± .07
Median (mmHg)	89± 13	92± 13	.98	<.0001	-3.3± 2.5

FIG. 5